

REMARKS

The Office Action mailed August 28, 2006 has been received and reviewed. The application is to be amended as previously set forth. The amendments are made without prejudice or disclaimer. No new matter has been entered. Claims 2-4, 6, 7, 14, 16, and 17 are pending in the application, all of which stand rejected. Reconsideration is respectfully requested.

1. 35 U.S.C. § 112, 2nd ¶

Applicants thank the Examiner for withdrawal of the 35 U.S.C. § 112, second paragraph rejections.

2. 35 U.S.C. § 102

Claims 2-4, 6, 7, 14, 16, and 17 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Cassol *et al.* (Mem. Inst. Oswaldo Cruz, Rio de Janeiro, 1996, 91(3):351-358) (hereinafter "Cassol").

Claim 2 as amended recites "quantifying the amount of the nucleic acid of interest present in the at least one sample." Support for the amendment may be found throughout the as-filed specification, such as at paragraph [0018]. Cassol does not determine the amount of nucleic acid of interest present in a sample. Cassol is concerned about what kinds of HIV mutations occur most frequently, but no information is provided about the amount of nucleic acid of interest in a sample. Therefore, Cassol does not anticipate claim 2. Likewise, claims 3, 4, 6, 7, 14, 16, and 17 are novel for at least the reason of depending from claim 2. Applicants respectfully request withdrawal of the 35 U.S.C. § 102 rejections.

3. 35 U.S.C. § 103

Claims 2, 6, 14, 16, and 17 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Moye *et al.* ("Detection and Quantitation of HIV-1 RNA from Filter Paper Adsorbed Whole Blood or Plasma by NASBA Isothermal Amplification," 4th Conference on Retroviruses and Opportunistic Infections, 1997, Abstract) (hereinafter "Moye"). Specifically, it was thought that Moye discloses detection and quantification of HIV-1 RNA. *Office Action mailed August 28, 2006, p. 5.*

Applicants respectfully submit that Moye does not disclose a method of quantifying nucleic acids of interest. An attempt was made by Moye to quantify HIV RNA of filter paper adsorbed dried whole blood (DBS) or plasma (DPS), but applicants submit that this attempt failed since no interpretable results were obtained. This is supported by the following table of the data provided in Moye.

	Mean \pm SD Material Inter- replicate \DELTA RNA	Mean \pm SD copies/ml	P-value
LP	0.03 ± 0.27	5.42 ± 0.56	
WB	0.60 ± 2.40	5.62 ± 0.62	
DBS O/N	1.62 ± 2.96	4.60 ± 1.21	0.198
DPS O/N	1.26 ± 2.85	4.01 ± 2.28	0.056
DBS 15 min	1.84 ± 2.42	3.14 ± 2.36	0.005
DPS 15 min	0.24 ± 1.90	4.55 ± 1.22	0.175

- The second column represents mean values with a reported uncertainty greater than the mean values themselves. These “results” mean that the true values may as well be zero in each case of the second column.
- The third column represents mean values with a reported large uncertainty. This means that the mean values are each taken from several measured values which are widely dispersed. The uncertainty of the mean values is so large that almost any HIV RNA amount in a blood sample of an HIV-infected individual will fall within the range. For instance, with the DPS O/N (plasma spotted on filter paper, dried overnight) a mean value of 4.01 ± 2.28 was obtained. Moye reports the mean values as log {10} values. This means that the mean value of $10^{4.01}$ RNA copies/ml has an uncertainty range of about $10^2 - 10^6$. Hence, the RNA amount is somewhere between 100 and 1,000,000 copies/ml. Any blood sample of an HIV-infected individual wherein HIV RNA is present is very likely to contain between 100 and 1,000,000 RNA copies/ml. However, the actual RNA amount still remains obscure. The conclusion that the amount of RNA is somewhere between 100 and 1,000,000 is not a quantification of RNA. This is the same kind of

“quantification” as a pregnancy test would be, wherein it is concluded the amount of children that a woman will give birth to is between 0 and 10.

- Three mean values (DBS O/N, DPS O/N, AND DPS 15 minute) have large p-values, meaning that there is no significant relationship between the individual measured values. A p-value indicates the probability (ranging from zero to one) that an obtained result is due to chance rather than a true relationship between measured results. Small p-values indicate that it is very unlikely that the results were due to chance. If p is 0.05, it means that there is a 5% chance that the relationship is due to chance rather than a true relationship. A p-value of 0.05 or less is the commonly used standard to determine whether a relationship between variables is significant. Hence, the three p-values of the DBS O/N, DPS O/N, AND DPS 15 minute measurements, which are larger than 0.05, indicate that there is no statistically significant relationship between the individual measured values. Therefore, the obtained mean values are not statistically significant.
- The only mean value with a p-value of less than 0.05 is the mean value of DBS 15 minute. This mean value is 3.14 ± 2.36 . However, this mean value is significantly different from the reference values LP and WB.

Moye did not succeed in quantifying RNA since mean values are obtained with such a large uncertainty that almost any HIV RNA blood content of an HIV-infected individual will fall within the uncertainty ranges. However, the actual RNA amount still remains obscure. Moreover, the obtained mean values are either statistically not significant (large p-values) or significantly different from the reference values. The only conclusion that can be drawn from Moye is that Moye did not quantify the RNA. This is even acknowledged by Moye themselves, since they draw the conclusion that “[w]ith further improvement in recovery and precision, this or similar methods could bring HIV-1 RNA quantitation to settings heretofore considered inaccessible.” (emphasis added).

Contrary to Moye, a method according to claim 2 does provide reliable results. This is for instance shown in Table 1 on page 15 of the as-filed specification of the present application.

200 μ L plasma of patient R02-05179 that had been directly added to lysis paper yielded an RNA amount of 3.84 whereas 200 μ L plasma or blood spotted on paper yielded an RNA amount of 3.86. The other values in Table 1 further confirm that a method according to claim 2 provides results that are comparable to direct nucleic acid measurements.

Moye did not succeed in quantifying RNA; therefore, Moye does not teach or suggest "quantifying the amount of the nucleic acid of interest present in the at least one sample" as recited in amended claim 2. Thus, Moye does not teach or suggest all of the elements of claim 2 and the claim is non-obvious. Likewise, claims 6, 14, 16, and 17 are non-obvious for at least the reason of depending from claim 2. Applicants respectfully request withdrawal of the 35 U.S.C. § 103 rejections.

If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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